

# Trihexyphenidyl Misuse in Delusional Disorder

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ABSTRACT

Trihexyphenidyl is an anticholinergic medication that is routinely used for the management of extrapyramidal symptoms in patients who receive antipsychotic medications. Trihexyphenidyl has been reported to be abused by some patients, who start to take it in increasing doses and tend to report a sensation of relaxation or pleasure with this medication. Hence, whether trihexyphenidyl should be considered a psychoactive substance and whether nonprescription misuse of this medication should be considered under the purview of substance use disorders need further clarity. We present here two cases of trihexyphenidyl misuse which developed in the context of persistent delusional disorders and highlight the challenges in diagnosis in such a situation.

**KEYWORDS:** *Delusional disorder, dependence, misuse, trihexyphenidyl*

## INTRODUCTION

Trihexyphenidyl is an anticholinergic medication that is routinely used for the management of extrapyramidal symptoms in patients who receive antipsychotic medications. Trihexyphenidyl has been reported to be abused by some patients, who start to take it in increasing doses and tend to report a sensation of relaxation or pleasure with this medication.<sup>[1,2]</sup> Hence, whether trihexyphenidyl should be considered a psychoactive substance and whether nonprescription misuse of this medication should be considered under the purview of substance use disorders need further clarity. We present here two cases of trihexyphenidyl misuse which developed in the context of persistent delusional disorders and highlight the challenges in diagnosis in such a situation.

## CASE REPORTS

### Case 1

A 32-year-old married male presented to our center with a history of multiple prescription medications misuse, which started after his marriage around 10 years back. The illness started with a doubt on the character of his wife, leading to tension, headache, anger outburst towards wife, following which he was put on combination of trifluoperazine (5 mg) and trihexyphenidyl (2 mg) by a private practitioner. Within few months, the conviction

on doubt toward his spouse reached a delusional level. Gradually, he kept on increasing the dose of the medication (up to 20 tablets/day) to be relaxed, free from tension, and have a sense of well-being. He would get these medications from shops showing his old medical prescriptions, and sometimes, even without prescriptions. He showed the features of intense desire to take the medication, diminished control, tolerance, preoccupation with the substance, and withdrawal in the form of restlessness, tachycardia, irritability, aggressiveness, headache, sweating, and sleep disturbances on cessation. In addition, he was also using tobacco and sedative hypnotic (clonazepam or alprazolam) in a dependent pattern. He was prescribed amitriptyline when he approached health-care providers with tension-type headache around 4 years back but did not reveal the use of other medications then. Subsequently, he would alternate between amitriptyline and sedatives depending on availability. He also used tramadol for 2 years which started due to an episode of abdominal pain which subsided after few days, but he continued taking it later with features of dependence in the form of craving, tolerance, and preoccupation with

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the substance and impaired control. Hence, when he approached our center, he was taking multiple tablets of trihexyphenidyl (with trifluoperazine), amitriptyline, tramadol, and tobacco.

### Case 2

A 32-year-old married male presented with nicotine dependence for 20 years, alcohol dependence for 18 years, opioid dependence syndrome in the form of injection pentazocine for 15 years, and benzodiazepines abuse for 15 years. Along with it, he was using combination of trifluoperazine (5 mg) and trihexyphenidyl (2 mg) about 20–30 tablets per day which he took over the course of 14 years and had stopped a year back. It was started by a private practitioner after he had symptoms of delusion of infidelity. He reported that this combination medication increased the “high” of other substances. Hence, he continued using it in increasing dose and would arrange these medications from local chemists without valid prescription and developed features of dependence in the form of craving, tolerance, preoccupation with substance, impaired control, and symptoms such as restlessness, irritability, sleep disturbance, and anxiety.

### DISCUSSION

Many centrally acting anticholinergic drugs such as biperiden, benztropine, procyclidine, and trihexyphenidyl are used in clinical practice for control of extrapyramidal side effects induced by neuroleptics.<sup>[3]</sup> These anticholinergics, especially trihexyphenidyl, have been related to two types of psychotropic effects: mood elevating, euphorogenic, and stimulating effect and toxic psychosis effect. Few risk factors such as advanced age, history of sedative-induced confusion, concurrent use of tricyclics or neuroleptics, and narcotic drug abuse have been reported to increase the likelihood of such effects.<sup>[4]</sup> In a study of 50 patients with chronic psychosis, the prevalence of anticholinergic misuse was 34%, and trihexyphenidyl was the most common anticholinergic implicated due to its propensity to produce a “high.”<sup>[5]</sup>

Here, in both the cases, patients were misusing many prescription medications among which combination medication misuse of trifluoperazine and trihexyphenidyl was prominent. The combination medication exists as trihexyphenidyl negates the extrapyramidal side effects of trifluoperazine, a typical antipsychotic agent. Although both the patients took combination medication, it is likely that trihexyphenidyl was the medication that produced the euphoric effect due to its anticholinergic properties. The withdrawal symptoms were not specific though some of them were similar to the withdrawal

symptoms mentioned in published literature which include tachycardia, restlessness, aggressiveness, lethargy, giddiness, sweating, anxiety, body ache, headache, and photophobia.<sup>[1,2,6]</sup>

The exact biochemical explanation regarding the misuse of these anticholinergic agents is still unclear. Although mesolimbic dopaminergic system (formed by the ventral tegmental area, the nucleus accumbens, and the prefrontal cortex) is the common final reward pathway for drug abuse, the cholinergic system may interfere in this reward pathway. Activation of muscarinic receptors can facilitate dopaminergic transmission which leads to release of dopamine in the nucleus accumbens. Hence, by inhibiting these muscarinic receptors, the anticholinergics may inhibit dopamine reuptake and storage. This mechanism could explain the euphoric effect of these anticholinergics.<sup>[7]</sup> A double-blind study in healthy volunteers found improvement in emotional status with biperiden, the effect being related to the personality features of the volunteers.<sup>[8]</sup>

Neuroleptic drugs have been shown to disrupt the reward pathway motivated by many positive reinforcers. The neuroleptics blunt the euphoric impact of reinforcers by selective attenuation of motivational arousal which is required for goal-directed behavior for subjective experience of pleasure.<sup>[9]</sup> Due to this, patients with psychotic illness tend to use stimulants such as coffee or nicotine or other substances with mood-enhancing properties.<sup>[3]</sup> One needs to be cognizant of the fact that trifluoperazine may also produce some nonspecific withdrawal features such as weakness, dysphoria, sleep disturbance, and irritability on cessation.<sup>[10,11]</sup> However, since trifluoperazine is a dopamine-blocking agent, it is unlikely to stimulate the mesolimbic/mesocortical dopaminergic reward circuit, which occurs with other dependence-producing substances.<sup>[10]</sup>

Considering the available literature and case characteristics, it seems more likely that trihexyphenidyl was the main drug that led to increased and nonprescription use of the medication. Based on the above properties, the WHO gave a consensus statement regarding the use of anticholinergics in psychiatry and concluded that the prophylactic use of these drugs is not recommended.<sup>[12]</sup> It suggested to withdraw anticholinergic drugs after 3 months, as drug-induced Parkinsonism tends to improve spontaneously over this time despite continued antipsychotic medication.

Strictly following the criteria of dependence of International Classification of Diseases 10 (ICD 10), a diagnosis of dependence may be entertained with

demonstration of features of craving, loss of control, tolerance to increasing doses, and preoccupation.

<sup>[13]</sup> However, whether a category of F19, i.e., mental and behavioral disorders due to multiple drug use and use of other psychoactive substances or F55 i.e. abuse of nondependence-producing substances would suit better would be a matter of contention. Although ICD-10 has a category for antidepressants abuse, there is still no place for anticholinergic medications such as trihexyphenidyl. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition has recognized the abuse potential of trihexyphenidyl and has kept it under “Other (or Unknown) Substance Use Disorder” category.

<sup>[14]</sup> The subsequent edition of ICD probably needs to take a look at the placement of trihexyphenidyl misuse in appropriate nosological category.

## CONCLUSION

The use of anticholinergics in psychiatry needs to be cautious in view of its misuse potential. In some cases, the use of anticholinergic medication is justified. However, the long-term administration of these drugs is unnecessary for many. Hence, a clinician should be vigilant about its misuse in the clinical setting.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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